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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/924,944	08/08/2001	Douglas C. Harnish	0630/1G704US2	2000

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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/924,944	HARNISH ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *12-24 and 26-40* is/are pending in the application.

4a) Of the above claim(s) *12-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/18/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/09/2004 has been entered.

Claims 12-24 remain withdrawn for reason of record. Claims 12-24, and 26-40 are pending. Claims 26-40 are examined on merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The Office action contains new grounds of rejection.

Claim Rejections - 35 USC § 103, Moot

The rejection of claims under 35 U.S.C. 103(a) as being unpatentable over Harnish et al of record (1998, J. Biol. Chem. vol. 273, pages 9270-8) and Ameis et al of record (1990, J. Biol. Chem. vol. 265, pages 6552-5) in view of either Landschultz et al., (CA of IDS filed on 03/17/04) or Birkenmeier et al., (CB of IDS filed on 03/17/04), and further in view of Norris et al of record (1995, J. Biol. Chem. vol. 270, pages 22777-82), US Pat 5,908,859 of record (June 1, 1999, or Dichek et al of record (1998, J. Biol. Chem. vol. 273, pages 1896-903) is moot because all of the rejected claims are cancelled.

Applicant argues Applicant's arguments with respect to now cancelled claims have been considered but are moot in view of the new ground(s) of rejection.

The Following Are New Grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 has the broad recitation "a mammalian cell", and the claim also recites "a hepatocarcinoma cell", which is the narrower statement of the range/limitation. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte*

Hall, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949).

Claim 39 is confusing because of "The expression vector of claim 39". It is not clear what the metes and bounds are. Review of claims 20-38 does not reveal any claims drawn to "an expression vector".

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using an isolated host cell comprising the claimed exogenous nucleic acid molecules, does not reasonably provide enablement for any host cell comprising the claimed exogenous nucleic acid molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 26-39 are broadly interpreted to encompass host cells, which are not isolated and are comprised within an organism. Thus, the claims encompass host cells that have been transfected with the claimed exogenous nucleic acid molecules that are comprised within a transgenic animal, including nonhuman or human animals and animals treated using gene therapy.

The teachings of the specification cannot be extrapolated to the enablement of the claimed invention because the amount of guidance, direction, and exemplification set forth therein would not be sufficient to enable the skilled artisan to have a reasonable expectation of success in making and using the claimed invention without the need to perform additional, and an undue amount of experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The specification discloses the claimed exogenous nucleic acid constructs can be introduced into primary cells including primary stem cells at page 11. Furthermore, the specification discloses the recombinant ER or C/EBP vectors can be incorporated into the genomic DNA at page 12. Then, at pages 12-13, the specification discloses that the preferred vectors are viral vectors, one example is adeno-associated virus commonly used for gene therapy at page 13, also discloses at page 13 lines 8-10 that "Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Thus, a specific tissue can be specifically targeted."

The specification does not provide a sufficient amount of guidance, direction, or exemplification to enable the skilled artisan to make or use host cells that are comprised within a non-human transgenic animal. In the art of producing transgenic animals, the phenotype of the resultant transgenic animal is not always predicable or viable. Houdebine (*Journal of Biotechnology* 1994, 34: 269-287) teaches the vectors to be used for directing the expression of transgenes in any given tissue, or in all tissues, must contain the appropriate regulatory regions. Houdebine teaches expression is heavily dependent on the site of integration in the host genome and the site of integration is presently unpredictable. Therefore, it is concluded that one of skill in the art would need to perform undue experimentation in order to make and use the claimed host comprised within a transgenic animal.

In addition, the specification does not teach provide a sufficient amount of guidance, direction, and exemplification to enable the skilled artisan to have a reasonable expectation of successfully producing host cells within a living organism, which comprise the claimed recombinant vectors, by gene transfer, or *gene therapy*. The art of gene therapy, i.e., the *in vivo* delivery genetic information to targeted cells within a body using naked DNA or viral vectors or by reintroducing *ex vivo* modified host cells into the body, is still in its infancy. Moreover, the art is highly unpredictable and its successful application has been hindered by numerous limitations, which the specification does not remedy and would preclude the skilled artisan from having a reasonable expectation of successfully making and using the claimed invention without need of performing an undue amount of experimentation.

For example, the teachings of the specification have not overcome the problems with *in vivo* delivery and expression. Verma et al. (*Nature* 1997, **389**: 239-242) teach that the Achilles heel of gene therapy is gene delivery. Verma et al. state that the ongoing problem is the inability to deliver genes efficiently and to obtain sustained expression. Similarly, Amalfitano et al. (*Current Gene Therapy* 2002, **2**: 111-133) teach that non-viral mediated transfer of DNA generally suffers from low transduction efficiencies. In addition, Amalfitano et al. discuss numerous limitations that have been encountered in using retroviral vectors to deliver DNA into a subject and teach the use of adenoviral vectors can be ineffective because of the induction of strong immune responses in the host to the viral vectors and direct acute and chronic toxicity caused by the vector itself.

In view of the preponderance of evidence establishing the state of the art, now and at the time the application was filed, and the level of unpredictability associated therewith, in the absence of a disclosure of an amount of guidance, direction, and exemplification that is reasonably commensurate in scope with the claims, it appears that skilled artisan could not make and use the claimed invention with a reasonable expectation of success without having the need to perform an undue amount of experimentation.

Amending the base claim 26 to insert "isolated" before "cell" can obviate these grounds of rejection.

Claims 26-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This new matter rejection is made because of the new limitation in claim 30, which says that the three different components of the base claim 26 are expressed from the same vector. However, the Office is not able to locate the support for the three different components, i.e. (i)-(iii). The base claim 26, and all dependent claims are also rejected because claim 30 makes clear that all of the recombinant cells in all of claim 26-40 are from "the same vector", which does not have support in the specification as originally filed. Applicant is kindly requested to point out the support in the specification as originally filed since the Office is not able to find the support.

Claim Rejections - 35 USC § 103

Claims 26, 27, and 30-40 are under 35 U.S.C. 103(a) as being unpatentable over Calkhoven et al (1997, Eur. J. Biochem. vol. 249, pages 113-120) in view of Ameis et al., of record (1990, J. Biol. Chem. vol. 265, pages 6552-5), further in view of Norris et al., of record (J. Biol. Chem., vol. 270, pages 22777-82).

Claims 26, 27, and 30-40 are interpreted as drawn to recombinant cell (more specifically a hepatocarcinoma cell, i.e., HepG2 cell containing 3 DNA constructs, i.e. 1) DNA construct expressing a estrogen receptor (more specifically human estrogen

receptor alpha (ER-alpha); 2) DNA construct expressing a transcription coactivator C/EBP; 3) a reporter construct linking various art-known reporters listed in claim 33 (more specifically luciferase in claim 34) to hepatic lipase promoter/enhancer that contains CCAAT element (more specifically –1557 to +43 of human HL gene in claim 32), wherein the DNA constructs of the base claim 26 are in the various art-known vectors (pET), wherein claim 40 is drawn to an assay system containing the recombinant cell of the claim 26 for screening useful compounds affecting the ERalpha and/or C/EBP dependent transcription activation of hepatic lipase promoter/enhancer in multi-well format capable of detecting the reporter being used. In summary, the claims are drawn to a recombinant cell per se with 3 exogenous nucleic acid molecules encoding two proteins i.e. a known reporter protein controlled by a HL promoter, a coactivator of transcription (estrogen receptor), and transcription enhancer binding protein of C/EBP.

Calkhoven et al., at page 116, right column, the last paragraph, Fig. 5B, and Fig. 6 (page 118) teach HepG2 recombinant cells containing 3 DNA constructs, i.e. 1) DNA construct expressing a estrogen receptor expressing a estrogen receptor; 2) DNA construct expressing a transcription coactivator C/EBP in pET expression vector (note under the heading "Expression plasmid" at page 114); 3) a reporter construct linking CAT reporter gene to nucleic acid element that the transcription coactivator C/EBP and ER bind to (i.e. the apoVLDL III promoter). Calkhoven et al., teach that C/EBP and estrogen receptor work together to express

Calkhoven et al., do not teach HL promoter or a luciferase reporter gene.

However, Ameis et al., at Fig. 3 (page 6554), and page 6555, left column, 1st paragraph teach that the human HL promoter contains "two CCAAT elements", and also Alu DNA repeats are present in 5' untranslated region of the human HL gene.

Norris et al., are cited to show that one of ordinary skill in the art would be motivated to screen ER responsive enhancer using a luciferase reporter gene. Norris et al., teach "estrogen is a key intracellular modulator" including "female cardiovascular tone" (note 1st sentence at page 22777), and also teach that "[b]ecause of its diverse biological functions and the implied complexity of its targets, there has been keen interest in defining the genes which are regulated by estrogen" (note 1st sentence of right column at page 22777), and also teach that the Alu consensus sequence (i.e. GGTCANNNTGGTCNNNNNNNNTCACC) that ER binds to as shown at Fig. 4 (page 22781), and also teach an assay system using luciferase at page 22778.

In summary, reviewing sequence of HL promoter disclosed by Ameis et al., "the hepatic lipase promoter is positioned proximal to the 5'end of human hepatic lipase coding region" as claimed in the instant claim 31, or "the hepatic lipase promoter comprises human hepatic lipase promoter region from –1557 to + 43, relative to the human hepatic coding region start site" as claimed in the instant claim 32 contains the consensus ER binding Alu site and the consensus CCAAT sites that C/EBP protein binds to.

Therefore, it would have been obvious to one of ordinary skill to make and use a recombinant cells containing the claimed 3 different DNA constructs with a reasonable expectation of success by taking out the replacing the apoVLDL II promoter of the

reporter construct of Calkhoven et al., with the HL promoter of Ameis et al., to arrive at an estrogen-dependent HL promoter-driven reporter gene. The skill in the art in making the claimed recombinant cell using a known nucleic acid sequence is very high. One of ordinary skill would be motivated to make and use an estrogen-dependent HL promoter-driven reporter gene given that the Alu repeat of the HL promoter at its 5' untranslated region (note at Fig. 3 legend of Ameis et al.) contains the consensus Alu consensus sequence (i.e. *GGTCA*NNNT*GGTC*NNNNNNNN*TGACC*) that ER binds to as shown at Fig. 4 of Norris et al., (page 22781). In other words, the sequence of *ggtca*-ggc-*tggtc*-tcgaactcc-*tgacc* located between –1057 and –957 of Fig. 3 of Ameis et al., belongs to the Alu consensus sequence for ER binding. One of ordinary skill would have been motivated to make and use the claimed recombinant cell for screening compounds regulating the hepatic lipase gene promoter, which contains both the ER responsive element, and C/EBP element since Norris et al., suggest that regulating ER responsive gene would be a good target in heart diseases and other lipid-metabolism-related diseases in women.

Claims 26-28 are under 35 U.S.C. 103(a) as being unpatentable over Calkhoven et al (1997, Eur. J. Biochem. vol. 249, pages 113-120) in view of Ameis et al., of record (1990, J. Biol. Chem. vol. 265, pages 6552-5), further in view of Norris et al., of record (J. Biol. Chem., vol. 270, pages 22777-82), and further in view of Harnish et al., of record (1998, J. Biol. Chem., vol. 273, pages 9270-8).

Claims 26-28 are interpreted as drawn to a recombinant cell per se with 3 exogenous nucleic acid molecules encoding two proteins i.e. a known reporter protein controlled by a HL promoter, a estrogen receptor alpha or beta, and transcription enhancer binding protein of C/EBP.

Note 103(a) rejection above for what Calhoven et al., Ameis et al., or Morris et al., teach. In summary, combination of Calhoven et al., Ameis et al., or Morris et al., teach recombinant cell per se with 3 exogenous nucleic acid molecules encoding two proteins i.e. a known reporter protein controlled by a HL promoter, a estrogen receptor, and transcription enhancer binding protein of C/EBP.

However, none of Calhoven et al., Ameis et al., or Morris et al., specifically points out estrogen receptor alpha or beta.

However, Harnish et al., at page 9270, right column, last paragraph, 1st line teach that estrogen receptor alpha or beta as claimed in instant claim 28 had been known well before the effective filing date of instant application.

Therefore, it would have been obvious to one of ordinary skill to make and use a recombinant cells containing the claimed 3 different DNA constructs with a reasonable expectation of success by using the known sequence of estrogen receptor alpha or beta since the skill in the art in making the claimed recombinant cell using a known nucleic acid sequence is very high.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-

272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
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PATENT EXAMINER